UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,828	06/27/2006	Carlos Garcia-Echeverria	33586-US-PCT	3954

75074 7590 02/17/2010

NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH, INC.
220 MASSACHUSETTS AVENUE
CAMBRIDGE, MA 02139

EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
02/17/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,828	GARCIA-ECHEVERRIA, CARLOS	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-14,18,21 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-14, 18, 21, 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the amendment filed on November 25, 2009.

Claims 2-14, 18, 21 and 23 are pending in this application.

Withdrawn Rejections/Objections:

Applicant is notified that any outstanding rejection/objection that is not expressly maintained in this office action has been withdrawn or rendered moot in view of applicant's amendments and/or remarks.

The following rejections are maintained:

1. Claims 18 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating breast cancer, does not reasonably provide enablement for a method for treating a disease which responds to inhibition of IGF-1R generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The reasons from the previous office action are incorporated here by reference.

Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant argues that 'the present claims are limited to inhibition of IGF-1R, and further restricted to compounds of formula (I)'. This is not, however, found to be persuasive, for the reasons already provided in the previous office action. The instant claims are drawn to "a method of treating a disease which responds to IGF-1R" and to 'a method of treating various types of tumors'. The use disclosed for the instantly claimed compounds of formula (I) in the

specification is as inhibitors of IGF-1R tyrosine kinase activity. Further, due to the IGF-1R inhibitory activity, the compounds are disclosed to be useful to treat a large list of diverse diseases, some of which are listed in page 6 of the specification. Therefore, the instantly recited activity relates to numerous diseases and the specification does not provide sufficient enablement for the method of treatment of all types of diseases encompassed by the instant claims. Test assays and procedures are provided in the specification in pages 33-35 are related to IGF-1R tyrosine kinase inhibition and it was concluded that the compounds of the invention exhibit inhibitory activity, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the diverse disorders of the instant claims. The diseases and disorders encompassed by the instant claims include various types of proliferative diseases, tumors, graft vessel diseases, xenotransplant vasculopathies, etc., some of which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same.

The state of the art of record is clearly indicative that more than routine experimentation is needed for one of ordinary skill in the art to practice the instantly claimed method. See for example, LeRoith et al. (Cancer Letters 2003) indicate that 'studies suggest a role for IGF-1 as a risk factor for breast, colorectal, and lung cancer, but its utility as a pragmatic marker is potentially limited by ethnic and gender factors' (see page 134). Further, the reference provides that: "It has been suggested that the IGF-1R itself can function as an oncogene, based upon the phenotype of fibroblasts overexpressing the IGF-1R. However, the relevance of this system to

human cancer in general is unclear" (see page 134). The article concludes with the remarks that: "A better understanding of this complex system will facilitate the development of novel approaches to diagnose and treat various human cancers" (see page 135). As can be seen from the above, the cited state of the art reference fails to establish the use of the instantly claimed compounds in the claimed methods, without the burden of undue experimentation for one of ordinary skill in the art.

As clearly explained in the previous office action, the instant claim encompasses, for example, treatment of all types of cancer, which can affect different organs and having different methods of inflammation or harm to the body, and different vulnerabilities. The development of the most efficacious strategy for the treatment of the claimed diseases is based on understanding the underlying mechanisms of each type of disease. Therefore, it is maintained that applicants have not provided sufficient test assays or data to support the instantly claimed treatment or other activity commensurate in scope with the claims, as of the filing date of the application.

When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006.

The breadth of applicant's enablement is not commensurate in scope with the claims, i.e., 'method of treating a disease which responds to inhibition of IGF-1R' which according to the specification relates to a method of treating numerous diseases, see for example, the disclosure at page 6. Contrary to applicant's arguments, the specification provides little or no guidance to practice the claimed methods.

(The specific reasons provided in the previous office action are incorporated here by reference).

One skilled in the art of medicinal therapy recognizes that there are complex interactions between individual genetic, developmental state, sex, dietary, environmental, drug, and lifestyle factors that contribute to the carcinogenic process, making it even more challenging to have a single therapeutic agent for the treatment of diverse diseases. Rigorously planned and executed clinical trials, incorporating measurement of appropriate biomarkers and pharmacodynamic endpoints are critical for selecting the optimal dose and schedule. A detailed understanding of the molecular mode of action of the specific receptor, alongside the elucidation of the molecular pathology of individual diseases is required to identify disease types and individual patients that may benefit most from treatment. It is also important to construct a pharmacologic audit trail linking molecular biomarkers and pharmacokinetic and pharmacodynamic parameters to receptor response endpoints. Therefore, it is maintained that the specification does not enable one of skill in the art to use the claimed therapeutic method commensurate in scope, as of the filing date of the application.

2. Claims 2-14, 18, 21 and 23 are rejected under 35 U.S.C. 103(a) as being obvious over Furet et al., WO 2004/005282. The reasons provided in the previous office action are incorporated here by reference.

Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant argues that 'the instant claims [[1]] 2 and 21 represent a number of differences with Furet reference, the biggest distinction is that the variable Z in the present claim

set is fixed as benzyloxy which is attached to the phenyl group in the meta position'. As provided in the previous office action, the reference teaches a genus of compounds and further discloses compounds falling with the genus. Further, as submitted by applicants, the instantly claimed compounds differ from the reference disclosed compound (for example, the compound of Example 23, depicted in page 13 of previous office action) by the position of the benzyloxy substituent. In other words, the instant claims require that the benzyloxy substituent is at the *meta*-position as compared to the *para*-position for the reference disclosed compound. The instantly claimed compounds are therefore, positional isomers of the reference disclosed compound. Further, the reference teaches the substituent $(Z)_n$- (wherein Z can be benzyloxy) at any of the available positions of the phenyl ring and therefore, teaches the equivalency of the ring positions. The reference compounds are taught to be useful as pharmaceutical agents for the treatment of proliferative diseases, such as breast cancer, etc., see pages 6-7 of the reference. Thus, the reference provides sufficient motivation to one of ordinary skill in the art to modify the reference disclosed compound and change the position of the benzyloxy substituent from the *para*-position to the *meta*-position. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such isomeric compounds are suggestive of one another and would be expected to share similar properties and therefore, the same use as taught for the reference compounds, i.e., as pharmaceutical agents.

Applicant cites *Takeda v. Alphapharm* to support the argument. However, the situation is *Takeda* is different from the instant case. The court in that case ruled that 'one of ordinary skill in the art would not have been prompted to modify the reference compound, using the steps of homologation **and** ring-walking, to synthesize the claimed compounds'. Contrary to the cited

Takeda ruling, in the instant application, one of ordinary skill in the art needs to modify the reference compound by changing the position of a single substituent on the phenyl ring.

Applicant argues that 'there remains a need to identify a reason why modification of the prior art would occur to get the presently claimed structures'. As previously provided, the reference teaches a genus of compounds that are useful as pharmaceutical agents and further, discloses several species falling within the genus. It would have been obvious to one of ordinary skill in the art to select any of the compounds falling within the genus of the reference, including those of the instant claims, with the reasonable expectation of obtaining compounds with similar properties and therefore, the same use as taught for the reference compounds. One of ordinary skill in the art would have been motivated to prepare compounds that are structurally analogous to the reference compounds, for example, by changing the position of the benzyloxy substituent of reference exemplified compound of Example 23, with the reasonable expectation of obtaining compounds having properties consistent with the properties of the reference compounds.

Applicant's arguments citing *KSR* are fully considered but they were not deemed to be persuasive. The prior art is not limited just to the reference being applied, but includes the understanding of one of ordinary skill in the art. "*KSR* forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness" *Ex parte Smith*, USPQ 2d (BPAI June 25, 2007).

3. Claims 2-14, 18, 21 and 23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over pending claims 1-11, 13 and 14 of copending Application No. 10/520,567 (now allowed).

It is acknowledged that applicant will address the rejection once allowable subject matter is indicated.

The following rejections are necessitated by the amendment:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-5 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3-5 and 23 depend from canceled claim, i.e., claim 1. It is suggested that the claims be amended to depend from a pending claim which provides antecedent basis for the claims, for example, claim 2. Appropriate correction is required.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Deepak Rao/
Primary Examiner
Art Unit 1624

February 17, 2010